Results of Pulmonary Resection: Sarcoma and Germ Cell Tumours

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Synopsis

Pulmonary metastasis can be present in as frequently as 88% and 80%, respectively, of patients with sarcoma and germ cell tumour with metastatic disease. In both sarcoma and germ cell tumour, pulmonary metastatectomy may be the only means of rendering a patient disease-free. Sublobar (wedge or segmentectomy), lobectomy, and, rarely, pneumonectomy can be safely performed to achieve complete resection. Bilateral disease can be resected via staged thoracoscopy/thoracotomy, median sternotomy, or clamshell thoracotomy. Finally, multiple resections and re-resections in select patients have resulted in improved survival. The main principle of pulmonary metastatectomy is complete resection. In the appropriately selected patient 5-yr survival rates of as high as 35-52% for sarcoma, and 80% for germ cell tumour can be realized.

Key points

- Patients with controlled primary site of disease, absent extra-thoracic (or if oligometastasis, other sites are controlled or controllable), sufficient pulmonary function and overall functional capacity to undergo pulmonary resection who have pulmonary metastases that can be completely resected are candidates for pulmonary metastatectomy.

- Patients undergoing pulmonary metastatectomy of osteosarcoma may have a 5-yr survival as high as 35-50%. The 5-year survival of patients undergoing resection of soft tissue sarcoma metastases has been reported to be as high as 35-52%.

- Large case series of pulmonary metastatectomy of nonseminomatous germ cell tumour (NSGCT) have reported 5-year survival rates greater than 80%.

- There are no randomized trials on pulmonary metastatectomy in patients with metastatic sarcoma or NSGCT. Survival rates are from case series of selected patients without observation control arms for comparison.

Introduction: Nature of the Problem

Pulmonary metastatectomy dates back to the 1880s (1). Sublobar resections, lobectomy and pneumonectomy were subsequently described in the setting of metastatic sarcoma, renal cell cancer and colon cancer (2, 3). Selection criteria for pulmonary metastatectomy were formally proposed in a case series of pulmonary metastatectomies by Alexander and Haight (4). Since then, with increasing supportive data pulmonary metastatectomy has become a widely accepted treatment modality for patients with metastatic disease.

As high as 88% of patients with sarcoma were found to have single-site pulmonary metastatic disease in a retrospective study by Huth and Eilber (5). In a case series from Memorial Sloan-Kettering Cancer Center, Billingsley reported that 73% of 230 patients with recurrent soft tissue sarcoma had recurrences that initially appeared in the lungs (6). Eight percent of patients with clinical Stage I nonseminomatous germ cell tumour (NSGCT) will develop pulmonary metastases. Additionally, an estimated 10-20% of patients with Stage III disease who were treated with cisplatin-based chemotherapy will have residual intrathoracic disease requiring mediastinal dissection or pulmonary metastatectomy (7). Pulmonary metastatectomy may be the only therapeutic option to render these patients disease-free.

Therapeutic Options and/or Surgical Technique

Following systemic therapy and confirmation of limited disease, therapeutic options for controlled pulmonary metastases include continued systemic chemotherapy, isolated lung perfusion or suffusion, radiofrequency ablation, stereotactic body radiation therapy, and

surgical resection. Isolated lung perfusion or suffusion, radiofrequency ablation, and stereotactic body radiation therapy will be covered more thoroughly elsewhere in this issue.

Patients being considered for pulmonary metastatectomy should meet the following criteria: (1) controlled primary site of disease, (2) absence of extrathoracic metastases (or, in cases of oligometastases, extrathoracic sites of metastases are controlled or controllable), (3) sufficient pulmonary reserve to tolerate the proposed pulmonary resection, (4) complete resection of all pulmonary metastatic disease can be achieved with proposed pulmonary resection. Pre-operative planning should include pulmonary function testing and an evaluation of the patient's ability to tolerate an operation. Special consideration should be taken for patients receiving certain chemotherapeutic agents (bleomycin, mitomycin C, busulfan, cyclophosphamide, carmustine, gefitinib, paclitaxel and methotrexate). These patients are at risk for drug-induced lung disease, including interstitial pneumonitis and fibrosis, hypersensitivity pneumonitis and acute pneumonia. Fractional inspired oxygen (FiO_2) should be minimized in order to minimize the risk of oxygen toxicity. Finally, patients should be required to engage in smoking cessation for at least 3 weeks prior to surgery in order to reduce the risk of postoperative pneumonia and other complications.

Pulmonary metastatectomy can be achieved via thoracoscopy or thoracotomy for unilateral disease. Patients with bilateral pulmonary metastases can undergo bilateral thoracoscopy/thoracotomy, median sternotomy or clamshell thoracotomy. Proponents of open resection argue that more pulmonary nodules can be identified with manual palpation (8-11). The identification of more nodules, however, does not translate to improved survival (12), and proponents of thoracoscopy argue that patients undergoing thoracotomy experience significantly more complications (11). The European Society of Thoracic Surgeons (ESTS)

working group addressed several key issues to take into consideration in this decision-making process (12). The ESTS considers open and thoracoscopic approaches equivalent, advising that surgeons should use the technique that the surgeon is most comfortable with. Additionally, there are no data demonstrating a difference in outcome between an initial policy of bilateral versus unilateral exploration or simultaneous versus staged approach in patients with known bilateral disease. Results from the ESTS working group survey suggested that an initial approach via median sternotomy is acceptable. In cases not suitable for median sternotomy--such as posterior lesions or patients with previous pulmonary resection--staged thoracotomy with a 3-6 week interval was recommended. Zheng and colleagues recommended a similar approach to pulmonary metastatectomy except that these authors were more supportive of a thoracoscopic approach (13).

Ultimately, the main principle of surgical resection of pulmonary metastases is complete resection. When possible, preservation of pulmonary function should be maximized by limiting resection. Peripheral nodules can be treated with a wedge resection. More central nodules may require a segmentectomy or lobectomy. Very rarely, a pneumonectomy may be necessary to achieve complete resection.

Clinical Outcomes

Sarcoma

In a study by the Cooperative Osteosarcoma Study group, 81% of patients with sarcoma presenting with metastatic disease had pulmonary metastases (14). Sixty-two percent of these patients have metastatic disease in the lungs only. As sarcoma often does not respond to

systemic or radiation therapy, complete resection with a pulmonary metastatectomy may be the only means by which to render a patient with single-site sarcoma metastasis free of disease.

There are few prospective studies and no randomized trials evaluating the role of pulmonary metastatectomy in the management of patients with osteogenic sarcoma. The first significant case series was described by Martini, whereupon the authors describe twenty-two patients who collectively underwent 59 procedures for the resection of 152 nodules (15). The authors reported a 3-yr survival rate of 45%. Similarly, in subsequent case series, Snyder and Putnam in their series of 21 and 39 patients, respectively, both reported 5-year survival rates of nearly 40% in patients with osteogenic sarcoma who underwent pulmonary metastatectomy (16, 17). The presence of three or fewer nodules on preoperative imaging was found to be the single most useful preoperative risk factor.

In more recent case series, Kim, *et al* published their results from Massachusetts General Hospital consisting of 97 patients who underwent pulmonary metastatectomy between June 2002 and December 2008 (18). They reported an overall 5-yr survival of 50.1% and noted that patients with a disease-free interval <12mths (p=0.001), two or more pulmonary metastases (p=0.0007), a lesion >3cm in diameter (p=0.017), and a positive resection margin (p=0.004) had a worse survival. Conversely, histology, tumour grade and use of chemotherapy were found to have no effect on survival. Authors from the University of California Los Angeles reported results from the sarcoma database including data from 47 patients with osteosarcoma. They found that on multivariable analysis age >45 years, disease-free interval <1yr, synchronous disease, thoracotomy, histology and performance of lobectomy were associated with poor overall survival (19). Moreover, patients with an increasing number of risk factors were associated with a poor overall survival (64% at 5 years for patients with 3 risk factors vs. 3% at 5

years for patients with 5 risk factors). Finally, a multi-institutional review of 39 pediatric cases of metastatic osteosarcoma presenting with pulmonary metastases more than one year after primary site diagnosis reported a post-resection event free survival of 33% at 5 years and post-resection survival of 56.8% at 5yrs (20). These authors concluded that long-term survivors in patients who presented with pulmonary metastases are possible (53% post-resection overall survival at 10 years). They endorsed pulmonary metastatectomy and reported that the addition chemotherapy did not add benefit.

Patients with soft tissue sarcoma are distinct from those with osteosarcoma. Soft tissue sarcomas are non-ossifying tumors arising from connective tissue elements. Approximately 23% of patients with soft tissue sarcoma will develop distant metastases (6). As with osteosarcoma, the lung is the most common metastatic site, accounting for up to 80% of metastases (21). Pulmonary metastatectomy, similarly, represents the only potentially curative treatment for patients with soft tissue sarcoma and pulmonary dissemination (22, 23).

The first soft tissue sarcoma pulmonary metastatectomy was described by Weinlechner, at which time 2 incidentally found lesions were removed during a resection of a chest wall sarcoma (24). Since then, Van Geel and Sardenberg have published their case series. Van Geel and colleagues reported a 5-year survival of 38% for patients with soft tissue sarcoma undergoing pulmonary metastatectomy in their case series of 255 patients (25). Sardenberg reported a 7.5-year survival rate of 34.7% (26). Finally, the authors at the University of Pennsylvania report 3-yr and 5-yr overall survival rates of 67% and 52%, respectively, from their series of 48 patients undergoing metastatectomy for soft tissue sarcoma (27). The authors do concede that their improved results compared to historical controls were likely due to careful patient selection. As with other primary sites, a longer disease-free interval (greater than 6

months) and fewer than 3 nodules are associated with a higher overall 5-year survival. Repeated pulmonary metastatectomy was also associated with improved survival (28, 29). However, patients with soft tissue sarcoma presenting with synchronous pulmonary metastasis were not found to benefit from metastatectomy, and thus should be considered for clinical trials (30, 31).

Treasure, *et al* performed a systematic review of published case series on pulmonary metastatectomy for sarcoma (32). Eighteen studies published between 1991 and 2010 were included, involving 1357 patients, 43% of whom underwent subsequent metastatectomy. The reported 5-year survival for patients with osteosarcoma was 34%. The reported 5-year survival for patients with soft tissue sarcoma was 25%. In comparison, the 5-year survival reported from data from the Thames Cancer Registry was 20-25% and 13-15% in patients with bone sarcoma and soft tissue sarcoma, respectively. Improved survival was associated with the presence of fewer metastatic lesion and longer disease-free intervals. The authors, however, were very implicit in stating that there was no evidence to support that survival improvement was attributable to metastatectomy as there were no controls nor was treatment randomized in any of the studies included in the review. The authors proposed that improved patient survival was a result of the process of patient selection and not an effect of metastatectomy. Aberg published similar views were previously (33, 34). The authors emphasize the need for randomized trials to determine the true, and not the perceived, effect of pulmonary metastatectomy.

Germ Cell Tumours

When discussing pulmonary metastatectomy for germ cell tumour (GCT), it is typically in reference to nonseminomatous germ cell tumour (NSGCT). Metastatectomy in seminoma has a

limited role, but has been advocated in the setting of residual masses $\geq$ 3cm (35). This is on account of the fact that viable disease or relapse in patients with seminoma has been noted in cases with residual masses $\geq$ 3cm at a rate of 27%, compared to a rate of 3% in cases with residual masses < 3cm or no residual masses on computed tomography (36). There are no reliable survival data on pulmonary metastatectomy for seminoma, however. The practice at Indiana University is to follow patients with residual disease with serial computed tomography, considering surgical intervention only in patients with growth of the residual mass in patients with teratoma on testicular pathology. Conversely, pulmonary metastatectomy in NSGCT is widely accepted with good long-term results. In fact, data from the international registry of lung metastasis identified patients with germ cell tumours ($p=0.04$) as being associated with a better prognosis than patients with pulmonary metastases from other malignancies.

Due to excellent results from effective chemotherapy therapy regimens, pulmonary metastatectomy for NSGCT currently serves an adjunct role in the treatment of patients with metastatic NSGCT. All patients with persistent pulmonary nodules on radiologic imaging following systemic therapy should be considered for resection. However, only 5-10% of patients with metastatic NSGCT will require pulmonary metastatectomy (37). Steyerber, *et al* reported that histology at residual retroperitoneal lymph node dissection (RPLND) was a strong predictor of histology at thoracotomy (38). However, several authors have reported pathology from residual RPLND to differ from pathology from residual pulmonary nodules in as high as 30% of cases (39-42). Therefore, pulmonary metastatectomy should be at least considered even in cases with necrosis or fibrosis on RPLND.

Five-year survival rates of as high as 79-87% were reported in early, small case series of less than forty patients (39, 41, 42). Memorial Sloan-Kettering Cancer Center published the first

single-institution large case series of 157 patients undergoing pulmonary metastatectomy for germ cell tumour (between July 1967 and May 1995). Forty-four percent of patients had viable tumour in the resected specimen, and 26% of patients had metastases to other sites. Overall 5-yr survival after pulmonary resection was 68%, but 82% for patients diagnosed after 1985, when cisplatin-based chemotherapy regimens for NSGCT were introduced (43). Persistent carcinoma in the specimen ($p<0.0001$), and concurrent metastases to non-pulmonary, visceral sites ($p=0.0069$) were negative prognostic factors.

In 2005, Kesler, *et al* reported Indiana University's series of patients with metastatic NSGCT, fifty-nine and 26 of whom had pulmonary metastases and both mediastinal and pulmonary metastases, respectively, as salvage therapy (44). Median survival was 5.6 years, and it was reported that after a mean follow-up of 5.1years 42.3% of patients were alive and without disease. Older age, pulmonary metastases (versus mediastinal metastases), and $\geq$ 4 total intrathoracic lesions were found to be significantly predictive of worse long-term survival. In 2011, Kesler, *et al* reported the complete series of 159 patients undergoing pulmonary metastatectomy and 136 patients undergoing both pulmonary and mediastinal metastatectomy (45). More than half (52.7%) of patients were noted to have teratoma, 21.5% had necrosis, 15% persistent NSGCT and 10.1% degenerative non-germ cell cancer. Median survival was 23.5 years and more than 68% of patients were alive without disease after a mean of 5.6years. Older age at dx ($p=0.001$), non-germ-cell cancer in testes specimen ($p=0.004$), residual disease ($p<0.001$) were significantly predictive of survival. Survival was the same in patients with hematogenous versus lymphatic metastases. Finally, the authors reported that residual pathology was the driving predictor of survival.

Simultaneous pulmonary metastatectomy and RPLND could be performed simultaneously with acceptable morbidity and mortality (46). Similarly, pulmonary metastatectomy via staged thoracotomy or clamshell thoracotomy have been described for bilateral pulmonary disease with low morbidity. However, Besse, *et al* suggests that in certain circumstances bilateral exploration could be avoided (47). The authors reported their results from a multi-institutional retrospective review of 71 patients with residual pulmonary lesion following cisplatin-based chemotherapy. Of 39 patients with bilateral pulmonary disease, 2 (5%) had discordant histologic results. Moreover, of 20 patients with necrosis on initial pulmonary metastatectomy, 1 (5%) had teratoma on the contralateral lung. The authors concluded that with 95% pathologic concordance rate between the two lungs, contralateral pulmonary metastatectomy could be avoided when complete necrosis is found on the initial side pulmonary resection.

Complications and Concerns

Complete pulmonary metastatectomy can be achieved with low morbidity and mortality. Surgical mortality is akin to pulmonary resection for other diagnoses (0-0.6%) (39, 41-43). A surgical mortality of <1% was reported in pulmonary metastatectomy in the Indiana University series (45). However, the majority of surgical mortalities were in patients undergoing simultaneous resection of pulmonary and mediastinal disease. The most commonly reported complications are pneumonia, respiratory failure, atrial fibrillation, prolonged air leak and prolonged ventilation (19). Chyle leaks can also occur in patients with NSGCT who are concurrently undergoing an extensive lymphadenectomy for residual mediastinal NSGCT lesions (45).

Summary

Pulmonary metastatectomy plays a central role in the treatment of patients with metastatic sarcoma and germ cell tumour. Five-year survival rates can be as high as 50% for patients with sarcoma and 80% for patients with NSGCT. These survival rates are significantly improved compared to historical controls. Current data in support of pulmonary metastatectomy for sarcoma and NSGCT, however, are derived from nonrandomized case series without observation controls. Therefore, the reported survival rates could be a reflection of patient selection bias as opposed to the true curative effect of pulmonary metastatectomy. Randomized trials (in a multi-institutional effort) or at least comparison with observation controls need to be performed.

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